January 9, 1950.

Dear Harriett:

Thank you very much for your letter. I do not often encounter a critic, like yourself, both sceptical and informed, and I am only sorry that we don't have better opportunities to lock horns.

Perhaps fortunately, my comments on your paper could not be included in the review article that I mentioned in my last letter. This has now been published, and you should receive a reprint shortly. On p. 18 there is a remark that "the more credible reports uniformly picture the acquisition of a genetic function,..." which I hope you will not take in reference to your recent work. The sentence was written before your papers were published, and I had in mind only Boivin's correction of the claim that he had seen a transformation in E. coli from sucrose+ to sucrose-, (although, of course, even this is not necessarily a "loss")).

You are certainly quite right that there is no unequivocal evidence on "general grounds" for differentiated genetic material, and that the persistence of a single residual molecule of the "phenotypic character" may be essential for genetic continuity in bacteria. However, since you accept the conclusion, there may not be much point in laboring an argument which at best is far from rigorous. I also agree with you also (and this is somewhat confessional) that some of us geneticists may sometimes emit an aroma of a "holier than thou" attitude about genetic problems in bacteriology. I think that an evangelistic spirit may have been justified in trying to put over that there is a problem of heredity and genetic continuity which has to be considered — and this has been especially true with the issue of adaptive mutations, for which admittedly there is little or no rigorous or final proof on either side, in any instance. Perhaps it will be enough if I remark only that the approach embodied in the JEM paper was merely a little negative, at a time when there is a body of evidence which should be examined, if not innocently accepted, concerning bacterial "genes". In my letter, I did not fully understand your general outlook.

You will perhaps, in respect to "allelism", admit to the same kind of error that I commit by dragging in "competition". At least as I understand it, allelism has the implication of mutual exclusion, which means very little in the present system. Origin by mutation is hardly enough, especially in a system whose genetic complexity is unknown. E.G., there would be little point to calling T2h an "allel" of T2, since, at best there is only a small part of the phage to which the criterion of allelism can be applied. But this is a small matter, and not one of a logical error, but just how confused the least penetrating of your readers can manage to be.

Your evidence on the role of R forms in the transformation of III-1 sounds very convincing, but it should be more emphatically presented in print. Is there any direct way of placing a lower limit on the proportion of R cells in the transformed cultures, and a lower limiton the numbers that would have

to be present to account for the results? I am willing to accept your conclusions, but even a strong chain has its weakest links, even if these hold too.

Your mention of the blocking effect of inactive DNA is especially interesting. What sort of preparations are these?

To turn to coli now, I don't see that we are so far apart. The two major problems, and points that we might dispute, are 1) the organization of the genetic material [spec. whether it is linear or otherwise], and 2) whether the nuclei carry the genes, i.e., whether the stained bodies really are nuclei. I am certainly myself a good deal less satisfied with the evidence for linearity than I was before the heterozygote segregations could be studied. I am still convinced, from "reversed cross" type of evidence applied here that the peturbations are mechanical (i.e., that they do not depend on which allel occupies a given locus), and if so they certainly might obscure linearity (or noh-linearity, if you prefer). This is something we have got to go into again in great detail. That the genes are segregated ordinarily in blocks is very clear, from data involving a great many factors, and on a larger scale than mentioned in the PNAS paper. It is also clear that exchanges occur, althoughnot nearly so frequently as to obscure the correlated segregations. I would be interested to hear from you what hypotheses other than linear linkage should be considered in interpreting such exchanges. They may or may not fit linearity in the last analysis (I am not sure whether this is provable without begging the question, with the material available.) But what else would make sense. The data definitely do not fit a Konversion idea, if applied to single gene units. If block conversions occur, I think that one finds that, formally, linearity is a special case, depending on the qssumptic made for correlated behavior of conversions. But linear or not, isn't this block of genes that you might call a cytoplasmic granule, just as well a chromosome?

The nuclear problem is a much more difficult one, and our only lead for the moment is a comparison of haploid and diploid cultures. This study has been started, and there is no question but that there are profound differences, which could be interpreted as a doubling of units. I am very suspicious of this, however, and I had better not say much more. Perhaps you will draw your own conclusions, and they will be limited, from personal inspection, if you visit here this Fall.

It certainly would be exciting to find a new mechanism of genetic recombination, perhaps a la gene pools in phage, or whatnot. I simply do not have the evidence for it in K-12, that you do in the pneumococcus, and it would certainly be as bad an error to have leaned in the opposite direction of non-conservative speculation, as it may have been to try to adopt an orthodox interpretation. I think, too, that it is all too easy to accuse one another of a reluctance to do experiments, and that neither of us would indulge in it if we knew each other better at work. The rationalization is really mostly a groundwork to try to suggest some more useful experiments that will decide an issue. Skoog has menioned the possibility of your visit, and we certainly hope that you can make it, and that we will see you. We shall be at Berkeley until early September, but will be back here by the 15th or so. With best regards,

Sincerely,

Joshua Lederberg